Scientific Abstract

Insulin-like growth factor-I (IGF-I) is a pleiotropic growth factor that is known to play an important role in the development, maintenance and regeneration of peripheral nerves and skeletal muscle. IGF-I has been shown to reduce axonal death following ischemic injury and to promote neurite outgrowth. Local synthesis of IGF-I in skeletal muscle has been implicated in the processes of reactive nerve sprouting, axonal growth and synaptogenesis following nerve injury and in regeneration and work induced hypertrophy of skeletal muscle. IGF-I protein has been investigated clinically as a therapeutic agent for various human diseases including type I and type II diabetes, cachexia, and neurodegenerative disorders. Although initial results indicated some therapeutic activity, systemic toxicities including hypoglycemia, fat depletion, splenomegaly and renomegaly were observed. The approach that we are developing is directed at expressing IGF-I in muscles to elicit a localized effect on peripheral neuropathy and focal muscle atrophy/weakness.

Non-viral gene therapy has been utilized safely and effectively in animal models for vaccination and for local and systemic delivery of recombinant proteins to elicit therapeutic effects. In this study, we will utilize non-viral gene therapy to achieve expression of recombinant human IGF-I in the flexor carpi ulnaris muscle of patients with cubital tunnel syndrome. This will be accomplished by introducing the recombinant human IGF-I (rhIGF-I) gene in a plasmid via a polyvinylpyrrolidone (PVP) carrier. We have developed a PVP-based gene delivery system that increases the efficiency of gene uptake into muscle 5 to 10-fold without toxicity to muscle. The human IGF-I plasmid contains a gene expression cassette with regulatory sequences derived from the chicken skeletal α-actin gene designed to restrict expression of rhIGF-I to myofibers within the injected muscle.

In this trial, we will study the safety and expression of the drug in humans. This is a phase I, block randomized, placebo-controlled, double-blinded dose rising study. Each subject will receive a single injection of the study drug (hIGF-I plasmid) and/or vehicle (PVP carrier) into the flexor carpi ulnaris (FCU) muscle of either the right or left forearm. Routine physical examinations, clinical chemistry, hematology, and RT-PCR studies will be performed to assess safety, tolerability, and gene expression.